#15 DMT 10-28-03

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application	:	Richard C. Deth
Application No.	:	09/550,103
Filed	:	April 14, 2000
Confirmation No.	:	8235
For	:	METHODS OF IDENTIFYING AND DETERMINING THE EFFECTIVENESS OF THERAPEUTIC PROCESSES OR AGENTS FOR THE DIAGNOSIS AND TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS
Examiner	:	Sandra Wegert
Attorney's Docket	:	NU-431AX

TC Art Unit: 1647

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I hereby certify that this correspondence is being sent via facsimile to Examiner Sandra L. Wegert, TC Art Unit 1647, Fax No. (703) 308-4242, on Oct. 23, 2003.

By: Holliday C. Heine
Holliday C. Heine, Ph.D.
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Attorney for Applicant(s)

* *

DECLARATION OF RICHARD C. DETH, PH.D.
UNDER 37 C.F.R. §1.132

Via Facsimile
After Final
Commissioner for Patents
Washington, D.C. 20231

I, Richard C. Deth, Ph.D., a citizen of the United States of America, residing at 1484 Beacon Street, Waban, Massachusetts 02468, declare the following:

1. I received my doctoral degree in Pharmacology from the University of Miami (Florida) in 1975. I am currently a Professor of Pharmacology at Northeastern University in Boston, Massachusetts.

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2. I specialize in the study of signaling pathways involving G protein-coupled receptors such as the D_4 dopamine receptor. My particular interest is focused on folate-dependent methylation reactions, their control by dopamine and growth factors, and their involvement in various mental illnesses.

3. I am an inventor of the subject matter set forth in the present, above-identified patent application.

4. I have read and am familiar with the prosecution history of the present application, including the Office Action dated May 20, 2003 (Paper No. 12).

5. The detailed action of the Office Action rejects claims 5-9 under 35 U.S.C. §112, first paragraph, because "the Specification, while being enabling for a method identifying therapeutic agents for neuropsychiatric diseases involving the D_4 receptor and in which phospholipid methylation has been shown to be affected, does not reasonably provide enablement for agents or processes involving other neuropsychiatric diseases in which a clear link from the D_4 receptor to phospholipid methylation has not been established."

6. This declaration provides support that the specification is enabling for methods of identifying agents or processes for treating neuropsychiatric disorders, in addition to schizophrenia, in which there is a link from the dopamine D_4 receptor to phospholipid methylation. Specifically, given the theory behind the methods of the invention as proposed by the Applicant and described in the specification and given the state of general

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knowledge at the time the instant application was filed concerning the likely causes of other neuropsychiatric diseases related to schizophrenia, those of ordinary skill in the art would have believed that the Applicant's experimental showings with respect to schizophrenia were directly relatable to other neuropsychiatric diseases. Herein below are descriptions of exemplary neuropsychiatric disorders or diseases involving changes in D_4 receptor-linked phospholipid methylation.

7. An exemplary neuropsychiatric disorder is autism. From what was known about the causes of autism at the time this application was filed, it is my opinion that one of ordinary skill in the art would accept my assertion that the methods of the invention would be useful in identifying agents or processes for treating autism. Autism can be caused by genetic mutations (such as those impairing the adenosylsuccinate lyase enzyme in the purine synthesis pathway[1,2]) that result in the diversion of single-carbon groups away from the folate pathway. As I have now shown, this type of diversion results in a deficit in the availability of 5-methyl tetrahydrofolate for folate-dependent methylation of the dopamine D_4 receptor and subsequent D_4 receptor-mediated phospholipid methylation. Thus, it would be considered credible by those of ordinary skill that detection of a change in the level of dopamine D_4 receptor-mediated phospholipid methylation could be used as an assay system for candidate agents for the treatment of autism, as claimed in the instant application.

8. Adenosylsuccinate lyase mutations, as discussed above, cause preferential diversion of single-carbon groups from the

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folate pathway to purine synthesis. It is known that another developmental disorder, Lesch-Nyhan syndrome is also associated with excessive activity of the purine synthesis pathway[3]. Additional developmental disorders, including Fragile-X syndrome[4] and Angelman and Prader-Willi Syndromes[4], involve abnormal DNA methylation and gene silencing. Thus, developmental disorders as a group appear to involve abnormal folate-dependent methylation events, linking them to folate-dependent D_4 receptor-linked phospholipid methylation and to use of the assay system according to the invention as a screening tool for candidate therapeutic agents.

9. One of the hallmark symptoms of autism is impaired attention. This includes attention to other persons as well as impairment of attention-related learning[5]. This symptom is also common in schizophrenia[6] and, of course, attention-deficit hyperactivity disorder (ADHD). D_4 dopamine receptors have been linked to the risk of ADHD[7] and ADHD is widely recognized as a disorder of dopamine signaling [8], so diseases in which there is a deficit of attention are likely to be related to D_4 receptor-mediated phospholipid methylation. Thus, attention-deficit hyperactivity disorder can be considered as being a "schizophrenia-related disorder," since both disorders appear to include an important role for D_4 dopamine receptor-mediated phospholipid methylation.

10. Alzheimer's disease is associated with reduced levels of vitamin B-12[9,10], the required co-factor for methionine synthase that brings methyl groups from the folate pathway to the D_4 dopamine receptor. Treatment with 5-methyl tetrahydrofolate, the

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source of methyl groups for the D_4 receptor phospholipid methylation process, has been shown to improve dementia [11]. Levels of S-adenosylmethionine, a methyl donor, are lower in Alzheimer's disease[12]. Furthermore, the enzyme activity of methionine adenosyltransferase, required in the cycle of D_4 dopamine receptor-mediated phospholipid methylation, is reduced in Alzheimer's disease[13]. Thus, there is considerable evidence for impairments that involve D_4 receptor-mediated phospholipid methylation in Alzheimer's disease, such that it should also be considered as a "related neuropsychiatric disorder" in the context of the screening methods of the invention as claimed in the instant application.

11. Based on the foregoing and what is generally known in the art, those of ordinary skill would believe from what I have disclosed in the instant application that there is a sufficient correlation between changes in D_4 receptor-linked phospholipid methylation and other neuropsychiatric disorders related to schizophrenia that the screening methods claimed therein would be likely to generate candidate therapeutic agents or processes for these related disorders. The state of the art at the time of filing, when read with the knowledge of my results, indicates to those of ordinary skill that neuropsychiatric disorders related to schizophrenia, in general, involve changes in dopamine D_4 receptor-linked phospholipid methylation.

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Confirmation No.: 8235

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code, and that such willful false statements so made may jeopardize the validity of the document, or application, or any patent issuing thereon.

Signed this 30th day of September, 2003.

By: Richard C. Deth
Richard C. Deth, Ph.D.

Enclosure: *List of Cited References (Attached hereto)*

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